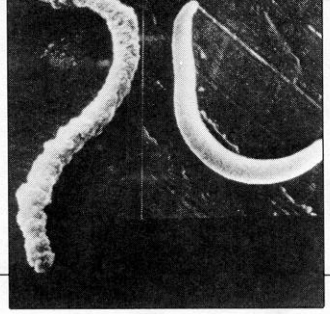


The crescent-shaped sporozoite stage of the malaria parasite, the form injected by a mosquito. The roughened surface of the sporozoite on the left is the result of attack by antibodies: a potential vaccine at work. Photo: New York University Medical Center.

MALARIA

THE KING IS THREATENED

NANCY JOHNSON SMITH

"The king of diseases," malaria, the single largest cause of disease and death in the world, received royal treatment in Calgary, Alberta, at the XI International Congress for Tropical Medicine and Malaria last fall. The congress, supported in part by IDRC, brought 1500 health professionals representing 68 countries to participate in almost 300 seminars and workshops covering all the major tropical diseases.

Thirty of the sessions dealt specifically with the malarial parasite and its *Anopheles* mosquito vector. Topics on malaria covered the entire spectrum of genetics, epidemiology, chemotherapy, health care delivery and training and, most publicized of all, vaccine development.

At the opening ceremonies, Nobel Prize winner Dr (Sir) Gustav Nossal, Director of the Walter and Eliza Hall Medical Research Institute, Victoria, Australia, set the theme: "Vaccines are history's most cost-effective public health tool. The importance of a malaria vaccine compares to that of the Salk vaccine."

Just how close the world is to enjoying such a health advancement was reported at the congress for vaccines to all three major stages of the parasite's complex life cycle.

However, in his opening address, Dr Adetokundo Lucas, Director of WHO's Special Program for Research and Training in Tropical Diseases (TDR), warned, "It would be hazardous even at this stage to attempt to predict when the first trial of a malarial vaccine will take place in humans, or when such vaccines could be expected to come into operational use. What can be said emphatically is that more progress has been made towards the development of malaria vaccines in the past decade than in the preceding 100 years."

Most advanced is the antisporozoite vaccine being developed by the team of Drs Ruth and Victor Nussensweig of New York University Medical Center (NYU) and groups at the National Institutes of Health and Walter Reed Army Institute of Research in Washington. The thread-like single-celled sporozoite is the stage of the *Plasmodium* parasite that enters the bloodstream when an infected mosquito bites.

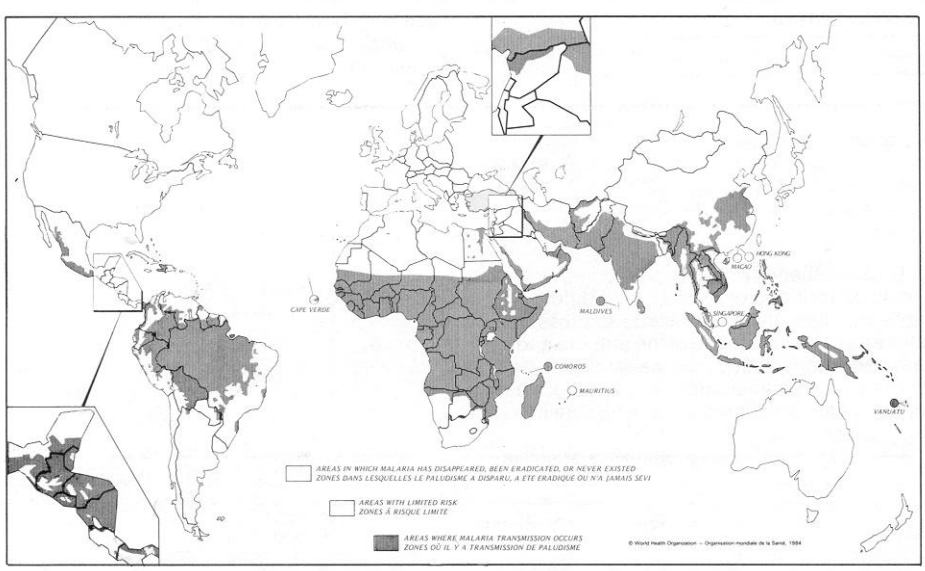
In several congress papers, Dr Ruth Nussensweig and members of her research team gave biotechnical details of their work that has led to the identification of the main antigen involved in stimulating the body's immune system to produce protective antibodies against sporozoites of *Plasmodium falciparum,* the most deadly of the human malarial parasites. Previously, this team identified similar antigen–antibody reactions for several other primate and human species of malaria.

The *falciparum* antigen is a "circumsporozoite" (CS) protein, part of a family of proteins that covers the whole surface membrane of the parasite. As was widely publicized in August of 1984, the NYU researchers reported they have also determined the biochemical nature of the antigen and the genetic code within the parasite's DNA that directs its production. Nussensweig further noted that, although the malarial antigen–antibody reactions appear to be species-specific, fortunately for the production of an effective vaccine, the several strains of *Plasmodium falciparum* around the world possess almost identical immunogenic antigens.

Critics of the vaccine have stated that sporozoites are in the blood stream for too short a time (several minutes) to stimulate an immune reaction before they penetrate liver cells and are protected from any further detection. In her discussion period, Nussensweig countered with a report that 90 percent of adults over 20 years old in heavily malaria-infested Gambia have antibodies to sporozoites. "That indicates a definite sporozoite-induced immune reaction," she said.

In her paper, Nussensweig suggested three possible methods for producing large enough amounts of antigen to be used for a vaccine. The NYU researchers have already synthesized the CS protein using conventional laboratory biochemistry. And, using genetic engineering techniques, they have inserted the antigen's gene into a strain of *E. coli* bacteria, which allows mass production of the antigen in the future. A third method would be to insert the antigen's gene into the DNA of vaccinia virus, used in the past to vaccinate against smallpox. In a later discussion, she suggested that her vaccine would be best administered to high-risk groups with little natural immunity to malaria, i.e., young children, pregnant women, and foreign travellers into an infested area. The NYU team will begin trials of the proto-vaccines in humans within the year.

Epidemiological assessment of status of malaria, 1982. Map: WHO



Life cycle of the malaria parasite, Plasmodium. *An infected* Anopheles *mosquito (below) bites a vulnerable host and injects sporozoites. Quickly, the sporozoites move through the bloodstream to the liver, where they change into schizonts. Then they emerge into the bloodstream again, invade and destroy red blood cells, and burst forth into the bloodstream as merozoites seeking new red blood cells to invade. A few parasites change into the gametocyte form and enter the bloodstream. If picked up by a mosquito these parasites can multiply and infect the next person the mosquito bites.*
Drawing: Carol Ann Morley

Such a sporozoite vaccine would protect against the initial malarial infection. But what would happen, critics ask, if a vaccinated person's immune system acted slightly sluggish and allowed a sporozoite to escape into a liver cell? One sporozoite alone is capable of dividing and releasing into the blood 30 000 merozoites, the parasite's second, asexual stage, which generates the actual malarial symptoms of chills and fever through cyclic invasions and destruction of red blood cells.

Because the sporozoite vaccine may not be totally effective, a second vaccine is being developed, reported Dr Robin F. Anders, Joint Head of the Malarial Team at the Walter and Eliza Hall Medical Research Institute, Victoria, Australia. One handicap in developing this vaccine, said Anders, is that, unlike the sporozoite stage, the asexual stage has demonstrated "a bewildering array of antigens on its surface," including a great deal of interstrain variability. Surface antigens differ even between parasite cells with the same DNA. Somehow the cells are turning on or off different sections of the DNA that codes for antigen protein. "A single clonal line can change its spots, so to speak," explained Dr Anders. Because of this complexity, researchers still have not isolated a single merozoite antigen that could serve alone as an effective vaccine. However, Anders said that his team "does have a number of antigens isolated and, among them, are several real candidates to use to make vaccine." In the next year they plan to begin monkey experiments to test the immunogenic action of these antigens.

Dr Nossal, director of this institute, cautioned that "a merozoite vaccine won't necessarily stop the disease completely. At the worst, a patient would have a less violent type of disease, maybe a transient headache." He noted that very likely the sporozoite and merozoite stage vaccines would be given in combination for best protection.

How far along is the second vaccine compared to the Nussensweig vaccine? " We'll be field testing in three years, probably," said Nossal. "The end of the decade is not an unrealistic time to expect us to have a ready vaccine. But we're a year or two behind Ruth Nussensweig."

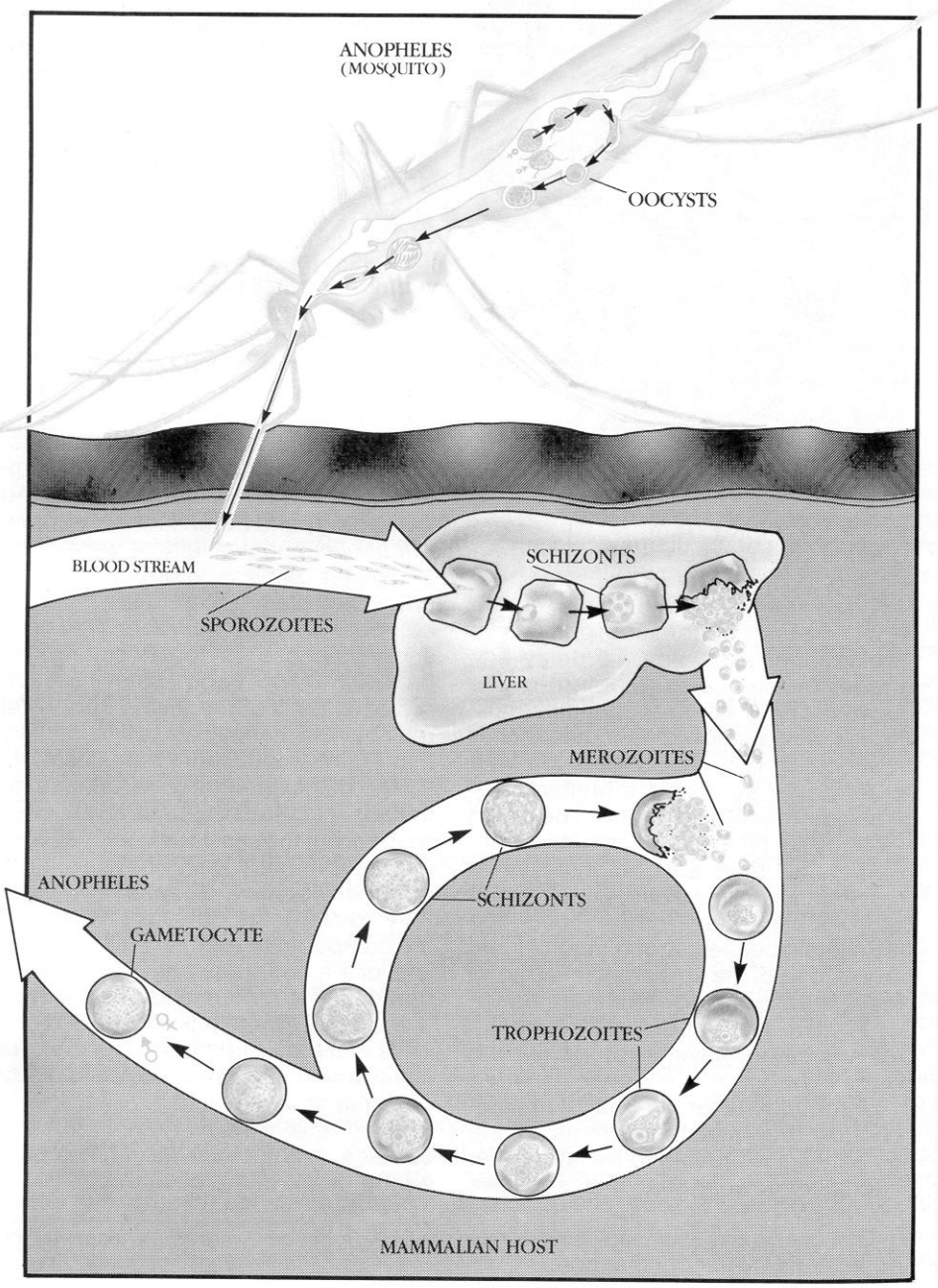
Progress on the development of a third "altruistic" vaccine was reported by Dr Geoffrey Targett of the University of London's School of Hygiene and Tropical Medicine. This vaccine would work against the sexual stage of malaria, transmitted to a mosquito when it feasts on an infected person. "This vaccine won't do the infected person any good," said Targett, "but it will stop transmission of the disease." The amount of antigenic variation in this parasite stage appears to be somewhere between that of the other two stages. Potential immunogenic antigens have been isolated for intensive *in vitro* and *in vivo* testing.

Scientists and health workers at the congress were cautious in their assessment of the potential vaccines because no one knows as yet their final properties, e.g., stability, mode of administration, or length of time they will convey immunity.

Dr Max Miller, congress president, said, "Immunization is the simplest way to prevent disease, but people shouldn't be too optimistic about malaria vaccines." For example, he pointed out, if the vaccines require a "cold chain," constant refrigeration, delivery in the rural tropics could be a major problem. "People are grabbed by the glamour of these vaccines but overlook the fact that unglamorous solutions are responsible for much of the health improvements in undeveloped countries."

In case vaccines are not the dreamed-for success, congress participants presented papers on a variety of other types of malarial control.

In the symposium on malarial chemotherapy and chemoprophylaxis, the session's chairman, Dr W. Peters, Head of Medical Protozoology at the University of London's School of Hygiene



IDRC JOINS THE BATTLE

With a budget of $2.6 million for 1984–85, the tropical and infectious diseases program is the second largest area of research supported by IDRC's Health Sciences Division. Over the years, support has been given for research into the etiology (causes), epidemiology (incidence and distribution), diagnosis, treatment, and control of a number of important tropical diseases. These include: schistosomiasis, trypanosomiasis (African and American), leishmaniasis, filariasis (including onchocerciasis), malaria, and leprosy.

IDRC has funded individual research projects on all but two of these diseases. In the case of malaria and leprosy, IDRC support has been channelled through the World Health Organization's Special Programme for Research and Training in Tropical Diseases.

In the area of infectious diseases, IDRC places much emphasis on studies of the etiology, epidemiology, and control of diarrheal disease, which continues to be a major killer of children under five. Research on acute respiratory infections and tuberculosis is also being advanced in all geographical regions. In addition, the growing incidence of the hemorrhagic variety of dengue fever during epidemics, especially in Southeast Asia and the Caribbean, has spawned a number of projects on the epidemiology and diagnosis of this sometimes fatal viral disease.

Within the tropical and infectious diseases program, IDRC is also supporting research into the increasingly serious problem of sexually transmitted disease (STD). At present, many developing countries do not have proper diagnostic and control programs in place. In the case of gonorrhea, the problem has been compounded, in some regions, by the spread of penicillin-resistant strains. IDRC-supported work has therefore focused mainly on the diagnosis and treatment of gonorrhea in Africa, Southeast Asia and, in particular, Latin America.

Finally, the tropical and infectious diseases program is supporting research on vaccines and vaccination programs. Important work in this area has included the development of a time-temperature indicator that allows health workers to tell at a glance whether a vaccine has spoiled or not. IDRC is also funding work on the development of improved yellow fever vaccine in South America and studies on the effectiveness of BCG vaccine for tuberculosis in Kenya, South Korea, India and Brazil.

and Tropical Medicine, stressed the growing problem of drug resistance. In the future, any new antimalarial drug will have to be used in combination with other antimalarials to slow down the development of resistance.

Reports on the geographical distribution of drug resistance showed that chloroquine-resistant *P. falciparum* strains have spread to all continents in the tropics. Cross-resistance to other antimalarials is also growing. In Africa, where a resistant strain was only detected in 1976, the number of malaria cases is increasing dramatically. On the Thailand–Kampuchean border, almost all *falciparum* isolates are resistant to chloroquine and generally Fansidar. In some areas this resistance even extends to quinine. Health workers are forced to treat many cases with the expensive combination of quinine and tetracycline. Thus the official WHO policy now is to restrict quinine use to keep it effective as a drug of last resort.

The face of malaria in Mexico
Photo: WHO

There were also disturbing reports from Thailand suggesting pockets of Mefloquine resistance. To delay any further resistance developing to this newest of the licensed antimalarials, health officials now plan to administer Mefloquine only in combination with other drugs, such as the Mefloquine–Fansidar formulation that will be registered by the end of 1984 as "Fansimef." Fortunately, there are no signs as yet of resistance to the still experimental drug halofantrine.

Several speakers urged much closer monitoring of the spread of falciparum resistance by using the new, easy-to-use "micro-kits" for detecting parasite resistance to several drugs in the field.

Unfortunately for the goal of malaria control, drug-resistant strains of the parasites are proving to be far hardier and faster growing than their sensitive relatives.

The best news was that still newer antimalarials are on the horizon, including derivatives of an ancient Chinese herbal medicine that seem to be effective against both *P. falciparum* and *P. vivax*, the milder human parasite responsible for relapsing malaria. Dr T.M. Cosgriff of the US Army's antimalarial drug program reported that the army is also testing 30 compounds that show a great deal of promise. And Dr W.E. Gutteridge of the Wellcome Foundation countered critics asserting that pharmaceutical companies are doing little antimalarial research by reporting on his survey of 16 internationally known companies. Results: eight companies are actively developing new drugs, five of them making final adjustments on specific drugs, such as eliminating side effects, or improving absorption.

In discussion, Dr W.H. Wernsdorfer, Chief of WHO's Malaria Research Unit, warned that the poorer countries will be the hardest hit if drug resistance is allowed to spread unchecked, forcing a shift from treatment with chloroquine to the next lowest-cost drug, which is still five times more expensive.

Later, London's Dr Peters reminded his audience that "it is vital that sole reliance should not be placed on drugs to limit the transmission of the pool of malaria." Instead he recommended more health education, more direct participation of communities in their own control programs, and vaccination.

Among the other methods of malaria control discussed at the congress was the less-human-oriented procedure of vector control. Several papers reported attempts to raise strains of genetically altered mosquitoes that were, for example, more resistant to malarial parasites, but these "pampered, petted" lab-bred strains have proven to be no match reproductively for wild mosquitoes. In general, researchers emphasized the importance of studying the ecology and behaviour of the many *Anopheles* species if there were to be any major gains in future vector control. Scientists are finding that species composition and numbers vary with such practices as forest cutting, urbanization and large-scale irrigation projects, but no one still is sure what really is the critical mosquito density that maintains malarial transmission.

The basis of innate resistance to malaria infections in humans was even probed, but the sessions demonstrated just how much we still have to learn about this ancient disease.

Yet despite the obvious difficulty of the campaign to reduce malaria, at the end of the congress participants were committed to continue. Dr Nossal concluded that "we're talking about a disease that's shaped human history over several million years. If we could eradicate malaria, it would be like killing one of the worst enemies of our species. It might have as much impact as the death of the dinosaurs." □

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